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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,875	08/21/2003	Ying-Fei Wei	PF174USD2	7047

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,875	WEI ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25 and 31-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25 and 31-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 2/23/07 have been fully considered but they are not persuasive.

Claims 25 and 31-44 are under consideration.

Specification

Applicant is again requested to amend the brief description of the drawings in the specification to reflect the numbered subparts.

The amendment filed 6/12/06 remains objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Amendments to page 5, line 3, paragraph [0027] of the specification.

This objection is maintained for reasons of record.

Applicant has altered amino acid end point ranges for different domains of SEQ ID NO: 2 as disclosed on page 5 stating that they are obvious typographical errors. This is not agreed with.

Applicant admits inconsistencies exist in numbering between the specification and sequence listing in PCT/US95/06386, particularly with respect to SEQ ID NO: 2.

The legal standard for obvious errors, based on the MPEP 2163.07(II), is that "An amendment to correct an obvious error does not constitute new matter where one

skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." So two elements are necessary to correct the error, (1) the determination that the skilled practitioner would recognize the existence of error and (2) the determination that the skilled practitioner would recognize the appropriate correction.

The cited case, In re Oda, states (see page 6, bottom of page to page 7) "Running through the foregoing discussion of the law is the clear and basic concept that *the invention* described in the original patent must not be changed. We note, first of all, that that is not a problem in this case. The invention before us, as defined in the claims, consists of three specific chemical compounds, there is no change proposed in the claims are in the description of the claimed compounds in the specification, there is no deviation whatever with respect to the invention."

From this discussion it is clear that when the invention (which is the claims) is at issue, it cannot be changed. In particular, the Oda court makes it clear that if the chemical compounds in the claims or specification were changed, this would be new matter. In Oda, the change was in how to make the chemical compounds and at page 7, it is clear that there were four independent bases to support an identification of the subject matter at issue.

Therefore, applying the first factor from the MPEP and In re Oda, it is clear that the skilled practitioner would have no way of recognizing the error from the specification and claims alone. From the originally filed specification, there is no reason to presume that the sequence endpoints of the soluble domain and transmembrane domain would be anything other than what was originally recited. It would only be by using information outside of the specification, information that is new matter, that one could determine that these endpoints might differ. For

the second factor, even if the practitioner recognized that the sequence description was flawed in some way, without outside information, the skilled practitioner would not be able to recognize the appropriate correction. Consequently, the error made in this application is not an obvious error, and the change which Applicant makes in the current claim set changes "the invention" in a way that the Court in In re Oda indicated would be a problem.

As set forth in the prior Office action, the original sequence listing for parent application PCT/US95/06386 numbered SEQ ID NO: 2 using negative numbers for the signal sequence (-45 through –1) and parent applications 08/930,564 and 09/227,853 (now U.S. Patent Nos. 6,410,506 and 6,642,006, respectively) altered the numbering of SEQ ID NO: 2 to remove the negative numbering and to begin numbering of SEQ ID NO: 2 at +1. This change was made in a substitute or amended sequence listing. The text of PCT/US95/06386 on page 6 is the same as that of the originally filed instant specification. PCT/US95/06386 does not refer to the negative numbering of SEQ ID NO: 2. The positions disclosed in PCT/US95/06386 on page 6 are considered to reflect the sequence disclosed in SEQ ID NO: 2 numbering from +1 at the first position rather than –45. This would have been a fair interpretation of the PCT/US95/06386 specification when read by one of ordinary skill in the art at the time of the invention. Thus, it reflects the present sequence listing for SEQ ID NO: 2 which explicitly numbers from +1 at the first position and does not provide basis for the altered ranges disclosed by applicant.

Applicant's arguments regarding the transmembrane portion and soluble region on pages 6-7 of the response are not persuasive. SEQ ID NO: 2 in PCT/US95/06385 used negative numbering for the signal sequence but the paragraph in question on page 5 of the specification

did not. The total size of the protein in SEQ ID NO: 2 of PCT/US95/06386 was not 329 amino acids. It was 374 amino acids.

Applicant's arguments regarding the soluble region on page 7 of the response are not persuasive.

Example 2 discusses nucleotide ranges with respect to SEQ ID NO: 1. The text indicates that particular ranges of SEQ ID NO: 1 include or exclude certain domains but does not identify any end points by either nucleotide or amino acid. Note that the instant specification on page 29 indicates that the putative soluble portion of the polypeptide corresponds to nucleotides 1100-1248 of SEQ ID NO: 1. The disclosure makes no mention of the primers with respect to the sequence of Figure 1 and the numbering of SEQ ID NO: 1 has not changed when the disclosure of PCT/US95/05386 and the instant application are compared. According to applicant's arguments with respect to Example 2, nucleotide 1248 is the last nucleotide of the soluble portion. This nucleotide is in the middle of the codon for the amino acid Tyr at position 309 of SEQ ID NO: 2. At the very least it is unclear whether this page indicates that amino acid 309 is included or excluded from the soluble portion. Applicant's proposed correction also requires one to accept that the nucleotide range in Example 2 is correct and the original disclosure on page 5 is incorrect. Applicant's arguments require one to add +45 to certain (but not all) amino acid regions on page 5 to make the regions consistent. Applicant's arguments require one to arbitrarily decide which parts of the disclosure are in error and which are correct. This is not the standard for an obvious error with an obvious correction. It is further noted that the primers disclosed in Example 1 for the soluble form do not appear to correspond to the stated amino acid positions.

Inconsistencies cannot be characterized or corrected as obvious typographical errors unless the correction to the obvious typographical error is also clear. The originally filed specification does not make clear that the changes made by applicant are the obvious correction to any inconsistency. Applicant states "renumbering of SEQ ID NO: 2 gives the value 344 a reasonable meaning" is not a clear correction to an obvious error.

Again, review of parent application (US 6,642,006 and US 6,410,506) with respect to these points reveals that no similar amendments appear to have been proposed and no declaration evidence or other arguments appear to have been presented. The sequence listing of the instant application was transferred from the parent application. The instant drawings also correspond to those in the parent applications.

Finally, review of parent application 09/227,853 reveals that the utility of the protein of SEQ ID NO: 2 was established based on a later published reference to Horie et al. (Genomics, **67**:146-152, 2000). Horie et al. discloses and characterizes a protein identical to SEQ ID NO: 2. However, Figure 1C shows completely different amino acid ranges for the signal peptide, transmembrane region and so forth when compared to those originally disclosed in the instant application or the correction proposed by applicant.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

Claims 25 and 31-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter and written description rejection.

Claim 25 has been amended to be directed to a method for the treatment of a patient having need to inhibit TGFα-HII comprising administering an antibody that inhibits TGFα-HII and is capable of binding to a polypeptide comprising a member selected from the group consisting of amino acid ranges 1-374, 46-374, 1-309, 46-309, and 260-309 of SEQ ID NO: 2 as well as fragments thereof (see parts (g)-(i)).

Basis is not seen for the claimed methods.

The limitation that "an antibody inhibits TGFα-HII" is not synonymous with the disclosure pointed to on page 24 that the antibodies bind to and inactivate TGFα-HII.

Original claim 25 depended from claim 22 that was directed to a compound that inhibits activation of the polypeptide of claim 19. These claims did not contemplate administering therapeutic antibodies directed to particular parts of SEQ ID NO: 2 and no basis is seen in the specification for the presently claimed method. Furthermore, although original claim 19 does list the ranges 1-374 and 46-374 as well as a polypeptide encoded by the cDNA contained in ATCC Deposit No. 97160, no basis is seen for the other named ranges. (See also new matter objection to the specification above with respect to these amino acid ranges.) A discussion as to what amino acids are identified as the leader sequence or transmembrane sequence cannot be construed as providing basis for claiming antibodies that specifically bind to particular fragments or administering such antibodies for particular therapeutic purposes. A fair reading of the specification would not indicate that these antibodies were contemplated as being part of the invention. Furthermore, part (f) is considered to mean any fragment of the polypeptide encoded

by the cDNA contained in ATCC Deposit No. 97160 in view of the recitation "a polypeptide." The originally filed claims do not disclose administering antibodies such as those claimed. Original claim 21 is directed to antibodies against the protein of claim 19 and not a method of treatment. Claim 25 is directed to a method of treating a patient to inhibit TGFα-HII by administering the compound of claim 22. The compounds of claim 22 do not correspond to the antibodies presently being claimed.

The information concerning the deposit on page 6 of the specification does not make clear what cDNA sequence is actually contained in ATCC deposit number 97160. The disclosure implies that only the mature sequence is contained. Applicant asserted in the prosecution of parent application 09/227,853 that DNA encoding the full-length sequence of SEQ ID NO: 2 is present in the recited deposit.

It is noted that the specification has been amended to change the date of deposit of ATCC 97160 from 15 May 1995 to 24 May 1995. Applicant has altered the originally filed specification at pages 4, 28, 29, and 32 with respect to deposit information without supplying the supporting documentation from parent application 09/227,853. It is permissible to amend the specification to include post-filing date deposit information with a corroborating statement (see MPEP 2406.02) establishing that the biological material disclosed in the specification was in fact the material deposited at the later date. Applicant must supply copies of the same evidence presented in 09/227,853 to complete the instant application. These changes are considered to be new matter in the absence of this evidence.

Applicant's submission of a copy of the ATCC depository slip is insufficient. The Jian Ni Declaration under 1.132 was submitted 9/7/00 to support the insertion of this deposit information.

Again, because claims 25 and 36 recite ATCC 97160, this deposit is required for enablement of these claims. Applicant is reminded that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited materials will be made irrevocably available with no restrictions upon issuance of a patent. These criteria have not been met in the instant application.

Claims 25 and 31-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

This rejection is maintained for reasons of record.

Applicant argues particular conditions that are disclosed in the specification as being suitable for treatment with the recited antibodies. These conditions are not limitations of the claims and the claims embrace many other unidentified conditions.

The specification fails to identify any antibodies that bind to any portion of SEQ ID NO: 2 that are capable of inhibiting TGFα-HII either in vitro or in vivo. The specification and prior art of record fail to provide any evidence that there is a correlation between any in vitro antibody binding and any in vivo inhibition of TGFα-HII for any therapeutic purpose.

The specification fails to identify any fragments of SEQ ID NO:2 (including any 30 and 50 contiguous amino acid ranges) that could be used to generate antibodies that have the property of in vivo inhibition of TGFα-HII for any therapeutic purpose.

General teachings on antibody production are insufficient.

In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The claims are broad, the amount of direction or guidance presented is limited, and there are no working examples of any antibodies nor any examples of administering antibodies for any purpose in vivo or in vitro. As such, one of ordinary skill in the art would have been required to engage in extensive experimentation to produce antibodies appropriate for the claimed method of treatment. While those of ordinary skill in the art knew how to produce antibodies generally, there is no guidance or predictability with respect to those antibodies or epitopes likely to provide operable embodiments.

Note that while the specification produces the full-length protein recombinantly, no biological activity is established for the full-length protein or any of the fragments thereof. As such, there is no guidance on how to assay for antibodies inhibiting TGFα-HII activity.

In the absence of such guidance or direction, it would constitute undue experimentation to practice the invention as claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marianne P. Allen
Primary Examiner 5/9/07
Art Unit 1647

mpa